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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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TITLE OF THE INVENTION (280 characters max)

Optimizing Ventilatory Assist in Ventilator-Dependent Patients Using Electrical Activity of Respiratory Muscles

ENCLOSED APPLICATION PARTS *(check all that apply)*

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OPTIMIZING VENTILATORY ASSIST IN VENTILATOR-DEPENDENT PATIENTS USING ELECTRICAL ACTIVITY OF RESPIRATORY MUSCLES

FIELD OF THE INVENTION

The present invention relates to a method for determining an optimal level of ventilatory assist to a ventilator-dependent patient, using myoelectrical activity.

BACKGROUND OF THE INVENTION

Of the many factors that lead to respiratory muscle fatigue, the tension developed by the muscles [34] and the duration of a contraction [2] are particularly important. These two factors are contained in such indices as the tension-time index [3] and the pressure-time product [10, 20, 32, 35]. Bellemare and Grassino [3] showed a direct inverse relationship between the endurance time of a fatiguing diaphragm contraction and the rate of decay of the ratio of the high to low spectral components (H/L) of the diaphragm electrical activity (EAdi), indicating that the two are expressing progressive failure to sustain load. The force exerted by the muscle has been shown to be directly related to the rate of decay of the power spectrum center frequency (or H/L ratio), and the level at which it plateaus [16, 21, 28]. Such shifts in the power spectrum reflect a slowing in the muscle action potential conduction velocity [28, 38, 39], and constitute an early indication that, at the cellular level, such breathing patterns cannot be maintained indefinitely [3].

Hyperinflation, which impairs the length-tension relationship of the respiratory muscles, i.e. the transformation of the neural activation into a mechanical output or pressure, reduces the capacity of the respiratory

muscles to generate pressure (neuromechanical uncoupling), unless EAdi is increased. Studies have shown that when inspiratory pressure, flow and duty cycle remain constant, increases in end-expiratory lung volume (EELV) promote reductions in endurance time [33, 44] and sustainable pressures [11]. In an animal model, Tzelepis et al [44] proposed that under such conditions, diaphragm shortening would require greater excitation to generate a given sub-maximum tension, and that this increased activation might account for the greater contractile muscle fatigability observed at shorter muscle lengths.

The "optimal level" of partial ventilatory assist, with the aim to ensure adequate pulmonary ventilation while preserving inspiratory muscle function, is generally set on an empirical basis in the clinical setting. It has also been proposed that the optimum level could be determined from the lowest stable breathing frequency (f_B) achieved, i.e. without bradypnea or apnea. In the patients, this corresponded to 16.4 bpm (breaths per minute) and was associated with a tidal volume (V_T) of 11.8 ml/kg. However, mechanical lung modeling in that study demonstrated that such a level of support actually resulted in a total unloading of the respiratory muscles. Others have defined the optimum level of partial ventilatory assist as that which produces the lowest transdiaphragmatic pressure (P_{di}) swings and found that this was associated with a f_B of 19.7 bpm and a V_T of 11.7 ml/kg. The pressure P_{di} in the study was used as a marker of inspiratory effort. Jubran et al [20] defined an upper bound inspiratory pressure-time product <125 cm H_2O· s/min as the desirable level of inspiratory effort to be achieved during partial ventilatory assist. Although arbitrarily determined, the appropriateness of such a threshold was justified by the fact that it corresponded to a tension-time index (TT_{di}) that was well below that considered to signify impeding inspiratory muscle fatigue. The study found a high variability in pressure-time products between patients and demonstrated that a f_B < 30 bpm and V_T of 0.6 L were better determinants of an optimal level of inspiratory effort during partial ventilatory assist. Based on these breathing pattern findings, it is likely that the level of respiratory

muscle unloading provided by this method of optimizing partial ventilatory assist was lower than that of the above reviewed studies. Brochard et al [8] defined the optimal partial ventilatory assist level as the lowest level of ventilatory assist, which when implemented, maintained the highest level of diaphragmatic electrical activation without the occurrence of fatigue as evaluated via diaphragm EMG power spectrum analysis. Interestingly, such levels of partial ventilatory assist were associated with a f_B of 20-27 bpm and V_T of 8.0 ml/kg, values similar to those later reported by Jubran et al [20].

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for determining an optimal level of ventilatory assist to a ventilator-dependent patient, using myoelectrical activity. For that purpose and according to non-restrictive illustrative examples, the method uses one or a combination of the following relations:

- A first relation estimating the patient's diaphragmatic muscle force from the patient's EAdi;

- A second relation estimating the patient's diaphragmatic muscle force from spectral changes during diaphragm contraction and involving a critical force level above which muscle fatigue starts to develop;

- A third relation, deduced from the first and second relations and relating the patient's diaphragmatic muscle force to (a) the critical force level above which muscle fatigue starts to develop, and (b) values related either to the patient's EAdi or the spectral changes during diaphragm contraction; and

- A fourth relation relating the transdiaphragmatic pressure to either (a) the

patient's EAdi or (b) the spectral changes during diaphragm contraction.

The above relations will enable evaluation of many patient's respiratory features from measurements of values such as EAdi, gastric pressure, esophageal pressure, respiratory flow, etc. The evaluation of these patient's respiratory features will allow the medical professionals to better optimise the characteristics of assistance of a ventilator-dependent patient.

The foregoing and other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of illustrative embodiments thereof, given by way of example only with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1 is a schematic representation of a non limitative example of experimental setup. *Left*: A catheter-mounted multiple array esophageal electrode used to measure diaphragm electrical activity (EAdi) with balloons mounted upon it for measurement of esophageal pressure (P_{es}) and gastric pressure (P_{ga}) was passed transnasally and positioned at the gastro-esophageal junction. Airflow was measured with a pneumotachograph and tidal volume (V_T) was obtained by integrating inspiratory flow. *Right*: On-line display of the target transdiaphragmatic pressure P_{di} and the root-mean-square (RMS) of the EAdi.

Figure 2 illustrates examples of tracings of tidal volume (V_T), diaphragm electrical activity (EAdi), transdiaphragmatic pressure (P_{di}), esophageal pressure (P_{es}), and gastric pressure (P_{ga}) obtained in one subject during "volume" maneuvers and "expulsive" maneuvers performed during the

hereinafter reported study. The "volume" maneuver consisted of an end-inspiratory hold at an increased lung volume, which resulted in the generation of a low P_{di} (left tracing), whereas the two expulsive maneuvers were performed at end-expiratory lung volume targeting a low P_{di} (middle tracing) and high P_{di} (right tracing).

Figure 3 shows examples of bar graphs displaying drops in diaphragm power spectrum center frequency (CF_{di}), targeted levels of P_{di}, pressure-time product (PTP_{di}) and the associated electrical activation (EAdi) observed during the three maneuvers performed in the study. Bars are average values obtained for five subjects (± SD).

Figure 4 represents examples of graphs from one representative subject showing the center frequency (CF_{di}), root-means-square (RMS) of the EAdi and the diaphragm pressure-time product (PTP_{di}) plotted over time during the volume maneuver (circles) and the two expulsive maneuvers at EELV, one targeting a low P_{di} (squares) and the other a higher P_{di} (triangles).

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

The study was conducted to determine in humans whether an increased EAdi, with neuromechanical uncoupling, promotes greater reductions in the center frequency of the EAdi signal (CF_{di}), when the diaphragm pressure-time product (PTP_{di}) is kept constant. An additional aim of the study was to establish the extent to which PTP_{di} would need to be increased, in the presence of normal neuromechanical coupling, in order to reproduce the drop in CF_{di} observed with uncoupling.

More specifically, the study evaluated whether increased diaphragm activation induced by an increased lung volume promotes increased drops in the center frequency (CF_{di}) of the diaphragm's electrical activity (EAdi) when

pressure-time product (PTP_{di}) is kept constant. Five healthy subjects performed runs of intermittent quasi-static diaphragmatic contractions with a fixed breathing pattern. In separate runs, subjects targeted transdiaphragmatic pressures (P_{di}) by performing end-inspiratory holds at total lung capacity with the glottis open (neuromechanical uncoupling), and at end-expiratory lung volume by performing expulsive maneuvers (no neuromechanical uncoupling). Diaphragm activation and pressures were measured with an electrode array and with balloons mounted on an esophageal catheter, respectively. Reproducing a P_{di} of ≈31 cm H_2O during neuromechanical uncoupling (lung volume increased to 77.5% of the inspiratory capacity) increased EAdi from 25% to 61% of maximum ($P<0.001$) and resulted in a 17% greater drop in center frequency ($P=0.012$). In order to reproduce, in the absence of neuromechanical uncoupling, the decrease in center frequency observed during neuromechanical uncoupling, a two- fold increase in P_{di} and PTP_{di} was required. It was concluded that a constant pressure-time product does not guarantee that the center frequency of the diaphragm remains stable when activation is increased.

METHODS

Subjects

Five healthy volunteers (1 female, 4 males) with a mean age of 40.6 ± 8.0 years participated in the study. The study was approved by the Scientific and Ethical Committees of Sainte-Justine's Hospital and all subjects gave their informed consent.

Experimental protocol

While seated in an upright chair, and facing a computer monitor 1 (Figure 1), each subject 2 performed repeated maximal inspirations to total

lung capacity (TLC) in order to obtain three reproducible voluntary maximum EAdi values. Subjects 2 were subsequently asked to perform intermittent, near-isometric diaphragmatic contractions of 10 seconds duration, separated by 5 seconds relaxation periods in which free breathing was allowed. With visual feedback of transdiaphragmatic pressure (P_{di}), during two runs a low level of P_{di} was targeted, while a higher level was targeted during the third run. The duty cycle was imposed by a sound signal, and each run lasted until a plateau in CF_{di} was reached, or until the subject was no longer able to maintain the target P_{di}.

In order to obtain two different EAdi levels for the same target P_{di}, subjects were instructed to perform two different maneuvers:

1. Volume maneuver: Subjects inspired close to their TLC and produced a given level of P_{di} (Figure 2; left tracing). The P_{di} was maintained at this lung volume with the glottis open.

2. Expulsive maneuver: Subjects performed expulsive maneuvers in order to generate a target P_{di}. All expulsive maneuvers were performed at end-expiratory lung volume (EELV) (Figure 2; middle and right tracings).

After initially performing a volume maneuver run, subjects then performed two expulsive maneuver periods. One expulsive maneuver run targeted a P_{di} similar to that observed during the volume maneuver but requiring less EAdi, and the other targeted an increased P_{di} (to reproduce the CF_{di} observed during the volume maneuver). The volume maneuver was subsequently repeated once for retest purposes. Subjects rested for 20 minutes between all runs.

Instrumentation

Using the set-up of Figure 1, airflow and tidal volume were measured by the computer 4 through a pneumotachograph 3, EAdi was measured by the computer 4 through a linear array of electrodes such as 5 mounted on an esophageal catheter 6 inserted through a patient's nostril (or patient's mouth) until the electrodes 5 are positioned in the gastro-esophageal junction 10 of the patient's diaphragm 7, esophageal (P_{es}) and gastric (P_{ga}) pressures were measured by the computer 4 through gastric 8 and esophageal 9 balloons mounted on the cathether 6 on opposite sides of the array of electrodes 5. Transdiaphragmatic pressure (P_{di}) was obtained by the computer 4 by subtracting P_{es} from P_{ga}.

On-line automatic processing of EAdi

EAdi (calculated as the root-mean-square (RMS)) was acquired, processed and displayed on-line using a standardized methodology [4, 36, 41]. CF_{di} was evaluated for signal quality using established indices and criteria in accordance with Sinderby et al [40]. To avoid influence of power spectral shifts on EAdi signal strength, RMS was calculated on the spectral moment of order 1 (M1) which is insensitive to conduction velocity [6]. For more extensive review see Aldrich et al [1].

Off-line signal analysis

Inspiratory duration (T_I), total breath duration (T_{tot}), and breathing frequency (f_B), EAdi and pressures were determined using the P_{di} signal. The PTP_{di} was obtained by multiplying the area subtended by the P_{di} signal by the respiratory frequency. EAdi signal amplitude was expressed as a percentage of the voluntary maximum EAdi (obtained from TLC maneuvers) [37]. Variables were compared between each of the maneuvers performed using one-way repeated measurements analysis of variance (ANOVA) and post hoc contrasts of significant effects were performed using the Student-Newman-

Keuls test. Test-retest reliability of the P_{di}, EAdi and CF_{di} values obtained during the two volume maneuvers performed was evaluated by calculating the interclass correlation coefficient (ICC).

RESULTS

The subjects were able to perform all maneuvers and maintain the imposed duty cycle (P=0.93; one -way ANOVA) during all protocols (Table 1).

As shown in Table 1 and Figure 3, subjects were able to achieve and maintain similar target P_{di} levels during the volume maneuver (high lung volume) and the low-pressure expulsive maneuver (EELV) (P=0.99). During the volume maneuver, subjects inspired to an average of 77.5±11.1% of their inspiratory capacity. In order to generate the same PTP_{di} at different lung volumes, the volume maneuver (neuromechanical uncoupling) required an EAdi of 60±8% of maximum compared to 25±8% for the expulsive low-pressure maneuver (at EELV). As shown in Table 2 and Figure 3, despite a matching of the PTP_{di}, the volume maneuver promoted a 17% larger drop in the CF_{di} than the expulsive low-pressure maneuver (EELV). Figure 4 shows a time tracing from one representative subject, where CF_{di} declines more rapidly and to a greater extent during the volume maneuver (circles), which required a high EAdi for a similar PTP_{di} compared to the expulsive low-pressure maneuver.

In order to produce a similar drop in CF_{di} during the expulsive maneuver (EELV) as was observed during the volume maneuver, more than a two-fold increase in the target P_{di} (P=0.015) was required. This was associated with an increase in EAdi from 25±8 % to 44±9% of maximum (P=0.009) (Figure 3). As can be seen in Figure 4, the rate of decline of the CF_{di} was similar for the volume maneuver (circles) and the expulsive high-pressure maneuvers (triangles).

Presented in Table 3 are the values of P_{di}, EAdi and CF_{di} for the test-retest of the volume maneuver. During the retest, subjects successfully targeted a P_{di} that was similar to that generated during the initial volume maneuver (ICC=0.95). EAdi was also similar (ICC=0.93) as was the drop in CF_{di} (ICC=0.98).

DISCUSSION

The study evaluated intermittent static contractions maintained at two different lung volumes, in order to examine the effect of altered neuromechanical coupling and increased diaphragm electrical activation, on diaphragm sarcolemma excitability, assessed by changes in CF_{di}. It was found that, for a given targeted PTP_{di}, the drop in CF_{di} was greater when EAdi was increased by neuromechanical uncoupling, suggesting that the level of muscle activation influences CF_{di}.

Studies on the canine diaphragm have demonstrated that changes in CF_{di} are associated with changes in the mean action potential conduction velocity (APCV) [38], confirming previous mathematical models [29]. During muscle contractions, both CFdi and muscle fiber APCV depend to a smaller extent on the cable properties of the fiber, [38, 39], and to a larger extent on the muscle membrane excitability [17, 18, 29, 39]. The excitability of the muscle fiber membrane is dependent on the transmembrane gradient of potassium, and with increased muscle activation, efflux of potassium increases. In order to defend the extracellular potassium concentration (and hence, the membrane potential), the cell depends on the re-uptake of potassium, e.g. via the ATP (Adenosine TriPhosphate) dependent sodium/potassium pump [12], and washout via the blood circulation [25], i.e. diffusion of potassium from the extra-cellular space into the blood stream.

Regardless if blood flow is reduced [23, 31, 42], or the muscle activation is increased, as in the present work, the muscles electrical activity will indicate reduced membrane excitability, by shifts in the power spectrum toward lower frequencies. CF_{di} can also be affected by factors such as motor unit territory, number of fibers in the motor unit, dispersion in arrival times of the single contributions in the motor unit signal, dispersion in action potential conduction velocities between motor units that can cause the EAdi power spectrum to shift [4, 29]. However, given that these influences are minor in healthy muscles [30] and given that the test situation did not allow for much variability in the contractile pattern, it is unlikely that these influences had more than a minor impact on the results.

In the study, a constant P_{di} was targeted with a constant duty cycle at two different lung volumes, and it was therefore assumed that P_{di} hindrance to blood flow under those conditions remained relatively similar at the different muscle lengths [19]. However, in order to achieve the same target P_{di} at an increased lung volume, EAdi was increased, which represents an increase in energy demand/consumption as well as increased metabolic output (e.g. potassium efflux) from the cell. As can be seen in Figure 3, the rate of decline of CF_{di} at increased lung volume was significantly higher than that observed when the same pressure was targeted at **FRC** with lower EAdi. Vitro studies have also demonstrated that increased activation (i.e. demand), accomplished by increasing stimulation frequency of a muscle shortened to 70% of its optimum length, in order to obtain the same tension generated at optimum length, resulted in an increased fatigue in the shortened muscle [14]. The current study therefore demonstrates that the higher diaphragm activation required for generating the target P_{di} at an increased lung volume (neuromechanical uncoupling) influences the rate/extent to which CF_{di} decays. Further theoretical evidence for the impact of neuromechanical uncoupling on the CF_{di} is provided in the Appendix.

In the absence of neuromechanical uncoupling, an increase in P_{di} is always associated with an increase in EAdi. In the study, doubling of P_{di} at the same lung volume (i.e. FRC) was associated with an increase in EAdi from 25% to 44% of maximum. Beck et al [6] showed that EAdi (in absolute values) is closely related to P_{di}, such that activation increases (i.e. energy demand increases) when pressure increases (i.e. energy supply decreases). However, this relationship is altered when muscle length is changed. In such a circumstance, P_{di} continues to reflect EAdi only when the P_{di} is normalized to the maximum P_{di} obtained at each corresponding lung volumes [6]. It was previously shown that when the same EAdi is targeted at different lung volumes, the higher resulting P_{di} generated at FRC promotes a greater drop in CF_{di} than does the lower pressure produced at the higher lung volume [42]. Such results indicate that for a given neural activation, an increase in force or P_{di} reduces diaphragm excitability. Consequently, the use of the TT_{di} and pressure-time product as indices for predicting changes in the excitability of the diaphragm sarcolemma (as reflected by CF_{di}) is limited to conditions of constant neuromechanical coupling, where the diaphragm force generating capacity remains unaltered.

Consistent with previous studies [3, 16, 21, 28], doubling of the target P_{di} at FRC in the present study increased the rate of decline of the CF_{di} as well as the level to which it declined (Figures 3 and 4). This is partially explained by the increase in EAdi, as discussed above. However, it is also partially explained by the fact that:

i) diaphragm contractions with a high P_{di} tend to hinder blood flow (i.e. energy supply) relatively more than contractions producing a low P_{di} [19], and

ii) impaired blood flow to a muscle has the propensity to promote shifts in the electromyographic power spectrum toward lower frequencies [22, 30].

Methodological and technical aspects

In the study the contraction and relaxation periods were maintained at a fixed duration and therefore any potential influence of duty cycle on muscle function [2, 22] was controlled for. It must be emphasized that accurate physiological measurement of CF_{di} depends on being able to control for:

(a) changes in muscle-to-electrode distance,

(b) electrode positioning with respect to the muscle fiber direction and location,

(c) electrode configuration,

(d) signal to noise ratio,

(e) influence of cross-talk from other muscles (including the heart and the esophagus),

(f) electrode movement-induced artifacts [7, 36, 38, 39, 40].

In the study, the technology used to measure EAdi power spectrum includes all means and devices necessary to minimize these influences [1, 36, 40]. The findings that evoked muscle action potentials are influenced by changes in lung volume [5, 15] have contributed to the assumption of a potential inherent inaccuracy of measured EAdi amplitude [5, 15] and CF_{di} [5]. However, during mild voluntary muscle contractions that do not alter diaphragm membrane excitability, it has been shown that chest wall configuration/lung volume and changes in muscle length do not have an effect on EAdi and CF_{di} [5, 6, 7, 17, 39]. Therefore the above-discussed effect of chest wall configuration/lung volume likely did not have an impact on the results.

Another factor that could have influenced our results was the difference in the partitioning of esophageal and gastric pressures for the same P_{di} during the different maneuvers. In a previous study [42], where subjects targeted the same EAdi at high and low lung volumes, greater decreases in CF_{di} were

consistently observed at EELV (higher Pdi), regardless of whether subjects performed an expulsive (i.e. Pdi generated mainly by gastric pressure) or a Mueller maneuver (i.e. Pdi generated mainly by esophageal pressure) at EELV [42]. In a pilot trial to that study (unpublished observations), it was found that diaphragm contractions generating identical Pdi, duty cycle and EAdi, produced the same trajectory of decrease in CFdi, whether subjects performed expulsive or Mueller maneuvers. Therefore, it is not believed that differences in the partitioning of the esophageal and gastric pressures during the volume and pressure maneuvers in the current study had an effect on the outcomes observed.

Clinical implications

The results of the present study have direct implications to patients being weaned from mechanical ventilation. It is well known that patients undergoing a weaning trial may demonstrate dynamic changes in EELV (dynamic hyperinflation) [43], which similar to the study would alter the neuromechanical coupling of the diaphragm. In order to compensate for this uncoupling (i.e. maintain the same P_{di}), the patient would need to increase diaphragm activation. The combination of an increased activation, with an elevated P_{di} would, according to the present study, lead to decreased diaphragm CF_{di} (excitability), and possibly an increased respiratory effort sensation [42]. Shifts in the H/L ratio of the power spectrum of the diaphragm electrical activity have been reported in patients with respiratory failure in whom ventilatory assistance is removed [8, 13]. However, given that diaphragm weakness is prevalent in mechanically ventilated patients [24], and it remains to be determined at what combined levels of EAdi and P_{di} would affect CF_{di}.

Conclusion

The study shows that diaphragm activation is an important determinant of diaphragm membrane excitability, and changes in CF_{di}. Furthermore it shows that the pressure-time product and tension-time index cannot be considered as valid reflections of diaphragm energy consumption and/or sarcolemma excitability when neuromechanical coupling is altered.

Appendix

With data from the above investigation, the diaphragmatic muscle force can be estimated from myoelectric measurements in two ways. The first way is expressed with the equation:

$$F = \mu EAdi \qquad (1)$$

where F is the diaphragmatic muscle force, μ is a proportionality constant, and *EAdi* is a measure of the myoelectric signal strength of the diaphragm. Here the square root of the first power spectral moment is used since it represents the signal strength, which has been compensated for the influence of changes in the propagation velocity of the myoelectric action potentials [29].

The second way to estimate the diaphragmatic muscle force is from the spectral changes during diaphragm contraction. For a forceful periodic muscle loading, the initial center frequency CF_0 decreases to a final plateau value CF_∞ according to the equation [26]:

$$CF_\infty = CF_o(1-\kappa)T_D / [(1-\kappa)T_D + \kappa T_R] \qquad (2)$$

Here, κ is the duty cycle, i.e. the inspiration time in relation to the total time period, and T_R is the CF_{di} recovery time constant pertaining to an approximately exponential time curve which is rather independent of the muscle force [9]. The symbol T_D denotes the time constant for the decrease in

CF_{di}, which is related to the muscle force as [27]:

$$T_D = \eta/(F - F_C) \qquad (3)$$

In this equation η is a proportionality constant and F_C is a critical force level above which muscle fatigue starts to develop. Equation (2) is rearranged to obtain the experimentally determinable quantity:

$$Q = T_R/T_D = [(1-\kappa)/\kappa]\ [(CF_0 - CF_\infty)/CF_\infty] \qquad (4)$$

Equations (3) and (4) then give:

$$F = F_C + Q\eta/T_R \qquad (5)$$

Making equal the two force estimates of equations (1) and (5) the following relation is found:

$$\alpha EAdi - \beta - Q = 0 \qquad (6)$$

where

$$\alpha = \mu T_R/\eta \qquad (7)$$

and

$$\beta = F_C T_R/\eta \qquad (8)$$

Relation (6) represents a set of three equations (the three experimental conditions) with two unknowns. A fitting procedure with data from Table 4 (with simultaneous minimization of the relative errors in EAdi and Q) gives the

values $\alpha = 0.00417$ and $\beta = 0.0419$ with a relative fitting error of 0.24.

With α and β known, the experimental values of the force can be expressed in relation to the critical level for onset of deterioration of cell excitability. The two ways to describe this are obtained by rearrangement of equations (1) and (7), and equation (5), respectively, which gives:

$$\phi_I = (F / F_C)_I = \alpha EAdi / \beta \qquad (9)$$

and

$$\phi_{II} = (F / F_C)_{II} = 1 + Q / \beta \qquad (10)$$

These quantities have been determined and are listed in Table 4 together with their mean values ϕ_m.

The observed transdiaphragmatic pressure (P_{di}) is assumed to be related to the muscle force as:

$$P_{di} = F\,G \qquad (11)$$

where G is a geometrical factor taking into account that the diaphragm muscle changes its shape with the inspired volume. This factor is thus assumed to be the same during the expulsive maneuvers with low or high P_{di} generation performed at end-expiratory lung volume. As with the force relations, the transdiaphragmatic pressure can be expressed in two ways, relating to the myoelectric signal strength and to the fatigue induced spectral changes. Combining equations (1), (5), and (11) we obtain:

$$Pdi = \mu\ \ EAdi\ \ G \qquad (12)$$

and

$$Pdi = (F_C + Q\eta / T_R)G \qquad (13)$$

which is further developed (with equations (7) and (8)) into the two expressions:

$$\gamma_I = (G\eta / T_R)_I = Pdi/(\alpha \quad EAdi) \qquad (14)$$

and

$$\gamma_{II} = (G\eta / T_R)_{II} = Pdi/(\beta + Q) \qquad (15)$$

Numerical values, calculated for the two expressions, are given in Table 4 together with their mean values γ_m.

From the results, listed in Table 4, it can be concluded that the forces in relation to the critical level are approximately the same during the volume maneuver and the high pressure expulsive maneuver, which is also reflected in their deterioration of cell excitability, expressed by the factor Q. During all conditions the forces are above the critical level as seen in the factor ϕ_m. The geometrical dependence, expressed in the factor γ_m, is obviously the same during low pressure expulsive maneuver and high pressure expulsive maneuver, but is much less during the volume maneuver. The ratio between the γ values in the volume maneuver and the expulsive maneuver is 0.41. Since the η values and the T_R values are expected to be independent of the maneuvers, this means that also the G factors have the same ratio. This indicates a much lower efficiency to convert force into pressure during the volume maneuver. The tension time index, taking into account the timing and the pressure, is thus not sufficient to describe the complexity of fatigue

development. At least it has to be modified with a volume dependent correction factor. Better, though, are methods reflecting the deterioration of cell excitability and not the mechanical result of the contraction.

Electromyographic and mechanical methods to detect muscle fatigue

Based on the above results, methods to determine critical levels of muscle failure during periodic loading (such as respiration) are described. A number of equations relating certain physiological variables to each other are needed and they will be derived prior to the description of the methods.

Periodic muscle load characteristics

Consider a periodic muscle loading, such as the respiratory work, in which repeated muscle contractions alternate with muscle relaxations. The situation is characterized by the time period T_0 and its parts: the duration of each contraction T_1 and the duration of relaxation T_2 where:

$$T_0 = T_1 + T_2 \qquad (16)$$

In order to simplify the equations, the duty cycle κ is introduced as:

$$\kappa = T_1 / T_0 \qquad (17)$$

The mean force developed during the time interval T_1 is denoted F.

Myoelectric changes due to fatigue

Isometric fatiguing contractions cause the myoelectric center frequency CF to decrease exponentially from its resting value CF_0 with a time constant T_F. During recovery the center frequency returns gradually to its normal value

following an approximalety exponential course, described by the recovery time constant T_R. It should be observed that many other characteristics of the power spectrum of the myoelectric signal exhibit the same dependencies (such as the median frequency, the zero crossing density, the so-called hi-over-low value, etc.). The recovery time constant depends mostly on the density of capillaries in the muscle and is rather insensitive to the exerted force. The fatigue time constant is strongly dependent on the force when it exceeds a certain critical level F_C. The relation is:

$$T_F = \eta / (F - F_C) \qquad \text{for } F > F_C \qquad (18a)$$

and

$$T_F \rightarrow \infty \qquad \text{for } F \leq F_C \qquad (18b)$$

The combination of repeated work and recovery events causes the center frequency to decrease from the initial value to a final plateau value CF_∞, at which there is a balance between the metabolite production during work and wash-out during recovery. The plateau value is:

$$CF_\infty = CF_0 (1 - \kappa) T_F / [(1 - \kappa) T_F + \kappa T_R] \qquad (19)$$

Introducing the notations:

$$\Delta CF = CF_0 - CF_\infty \qquad (20)$$

and

$$\varepsilon = \Delta CF / CF_0 \qquad (21)$$

Equation (19) can then be rearranged to read:

$$\kappa = 1 / [1 + (T_R / T_F)(\Delta CF / CF_\infty)] \quad (22)$$

With the notation:

$$Q = T_R / T_F \quad (23)$$

it is found that:

$$Q = [(1 - \kappa) / \kappa] \Delta CF / CF_\infty \quad (24)$$

which is an experimentally measurable quantity.

Force and pressure

The force F can be determined for skeletal muscles working over joints without synergistic effects from other muscles. For the diaphragm muscle the force cannot be directly measured, rather the transdiaphragmatic pressure P_{di} is obtained as a proportional measure. The following relation could be used:

$$F = \mu E \quad (25)$$

where μ is a proportionality constant and E is the myoelectric signal strength, preferably based on the first spectral moment which is rather insensitive to metabolic changes caused by fatigue. The relation to the pressure is proportional but non-linear. This fact is taken into consideration by introducing the factor G(V) which is volume (V) dependent, i.e.:

$$P_{di} = F G(V) \quad (26)$$

Thus,

$$\mu G(V) = P_{di} / E \qquad (27)$$

which also is an experimentally measurable quantity.

Myoelectric signal strength and spectral changes

Rearrangement of equation (18a) and insertion of equations (23) and (25) gives:

$$\alpha E - \beta - Q = 0 \qquad (28)$$

where

$$\alpha = \mu T_R / \eta \qquad (29)$$

and

$$\beta = F_C T_R / \eta \qquad (30)$$

It can be observed that α is dependent (through the parameter μ) on the electrode geometry and placement in relation to the muscle, while the other parameters are rather constant for similar muscles.

Experiments under fatiguing conditions at any volume give corresponding values of E and Q (through the center frequency changes). A data fitting procedure (not regression) gives numerical values to α and β. With α and β known, an estimate of the muscle force F can be obtained in relation to its fatigue threshold value, i.e.:

$$F / F_C = E \alpha / \beta \qquad (31)$$

As long as F/F_c is smaller than one, isometric fatigue does not develop. That means that the signal strength should be lower than the critical value:

$$E < E_{ISOM} = \beta / \alpha \qquad (32)$$

For periodic muscle work, higher forces and signal levels are tolerable.

Spectral changes as indicators of tolerable concentration of metabolites

The relative spectral change ε, defined in equation (21), is an indirect measure of remaining concentration of metabolites in the muscle during periodic fatiguing contractions. It seems that the muscle very rapidly goes into an anaerobic metabolic state once the force is higher than F_c and that virtually all contractions above this level causes changes of the center frequency. Therefore it is likely that a certain small value of ε is tolerable as long as it is below a certain critical level, which we denote ε_C. With this critical value introduced into equation (22) and simultaneous use of equations (18a) and (23), it can be found that the condition for long term fatigue not occur to be:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C] T_R (F - F_C) / \eta\} \qquad (33)$$

This expression can be rearranged to give the force condition:

$$F < F_C + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)] \eta / T_R \qquad (34)$$

or, together with equation (30),

$$F < F_C \{1 + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)] / \beta\} \qquad (35)$$

Since the force in diaphragmatic contractions cannot be simply measured,

equations (33) to (35) are expressed as functions of the myoelectric signal strength and the transdiaphragmatic pressure. Use of equations (25) and (26) give for the myoelectric signal strength:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C] (\alpha E - \beta)\} \quad (36)$$

and

$$E < \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} / \alpha \quad (37)$$

and for the transdiaphragmatic pressure:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C] (\alpha P_{di} - \beta)\} \quad (38)$$

and

$$P_{di} < \mu G(V) \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} \quad (39)$$

Procedures

From equation (28) the coefficients α and β are determined with myoelectric data from fatigue tests (calibration). Fatigue test can be performed by either reducing the level of assist, or performing a short airway occlusion, while measuring the myoelectric activity during a few inspiratory attempts. To shorten and facilitate the fatigue test the subject could be encouraged to voluntarily increase his efforts. Such a test is routinely performed to determine the maximum inspiratory airway pressure.

If myoelectric monitoring is used (giving signal strength and duty cycle), the critical signal strength is calculated using equation (37).

If transdiaphragmatic pressure monitoring is used (giving pressure, flow/volume, and duty cycle), the critical pressure level is calculated by using equation (39). This requires knowledge about the geometrical G(V) dependence, which can be obtained from a calibration of the experimentally measurable quantity P_{di} / E as shown in equation (27).

This is performed by either continuously measuring the P_{di} through, for example, esophageal and gastric pressure sensors, and the volume through, for example, a flow meter. Geometrical dependence of inspiratory pressure can also be estimated by performing single or multiple breath airway occlusions at two lung volumes, e.g. end-inspiration and end expiration lung volumes, when the volume difference is measured with, for example, at least one flow meter.

Estimates of the critical level ε_C can be determined from the general experimental fact that fatigue does not occur below a duty cycle of 0.2 even at maximum muscle force and that the critical force level F_C is approximately 0.2 times the maximum force. Equation (33) then gives $\varepsilon_C \approx \beta/(\beta+8/9)$, or, since both ε_C and β are small quantities:

$$\varepsilon_C \approx \beta \qquad (40)$$

The gain of ventilatory assist should be adjusted at a level such that the myoelectric activity does not exceed that described in equation (37) (higher support suggest unnecessary muscle inactivation). However, myoelectric activity should not exceed that described in equation (32) (this level indicates the level for muscle fatigue during isometric contractions).

Although the present invention has been described in relation to non-restrictive illustrative embodiments thereof, it should be kept in mind that these embodiments can be modified without departing from the spirit of the present

invention. In particular but not exclusively, the present invention pertains not only to CFdi and RMS but also to other related measures. Similarly, the present invention is concerned with any method of mechanical ventilation, including negative pressure ventilation.

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Table 1. *Breathing pattern and targeted Pdi values during the three maneuvers performed.*

	Volume maneuver			Expulsive maneuver Low pressure		Expulsive maneuver High pressure	
Subject	Ti/Ttot	VT%IC	Pdi	Ti/Ttot	Pdi	Ti/Ttot	Pdi
1	0.66	89.2	47.8	0.66	45.1	0.67	77.3
2	0.66	65.6	25.3	0.67	26.6	0.66	93.3
3	0.67	68.3	10.2	0.65	11.6	0.66	39.3
4	0.67	88.8	38.6	0.66	39.8	0.64	77.3
5	0.65	75.5	34.1	0.67	35.0	0.67	50.3
Mean (±SD)	0.66 (0.01)	77.5 (11.1)	31.2 (14.2)	0.66 (0.01)	31.6 (13.1)	0.66 (0.01)	67.5 (22.0)

Values are means for each subject of all the maneuvers performed. Ti/Ttot, duty cycle; Pdi, transdiaphragmatic pressure, V_T, tidal volume; IC, inspiratory capacity. All subjects were able to maintain the imposed duty cycle.

Table 2. *Individual CFdi values observed at end of each maneuver.*

Subject	Volume maneuver	Expulsive maneuver Low pressure	Expulsive maneuver High pressure
1	68.3 ± 8.7	81.3 ± 7.9	61.6 ± 5.6
2	67.4 ± 4.5	86.7 ± 8.0	70.5 ± 13.2
3	82.0 ± 12.3	94.3 ± 7.8	71.5 ± 5.0
4	72.8 ± 5.8	89.4 ± 6.1	73.4 ± 3.1
5	80.4 ± 9.3	104.1 ± 4.4	83.6 ± 5.4
Mean ± SD	74.2±6.8	91.2±8.6	72.1±7.9

Values are means for each subject for each of the maneuvers performed.

Table 3. ***Test-retest of the volume maneuver***

	$CFdi_0$ (Hz)		$CFdi_\infty$ (Hz)		EAdi (% max)		Pdi (cm H_2O)	
Subject	**Vol1**	**Vol2**	**Vol1**	**Vol2**	**Vol1**	**Vol2**	**Vol1**	**Vol2**
1	90.4	93.1	68.3	66.2	46.5	38.1	47.8	44.6
2	102.5	108.2	67.4	65.7	42.4	44.4	38.6	38.3
3	94.7	100.3	82.0	84.7	49.8	55.0	34.1	30.7
4	99.7	99.5	72.6	72.1	51.3	50.6	36.5	35.8
Mean (± SD)	96.8 (5.4)	100.3 (6.2)	72.8 (6.7)	71.9 (8.8)	66.7 (10.7)	65.0 (11.9)	25.3 (9.4)	29.5 (7.0)
ICC	0.94		0.98		0.93		0.95	

EAdi, diaphragm electrical activity calculated as root-mean-square; $CFdi_0$, baseline center frequency determined during resting breathing; $CFdi_\infty$, plateau value of the center frequency at the end of the volume maneuver; Pdi, transdiaphragmatic pressure, Vol1, first volume maneuver performed, Vol2, second volume maneuver performed, ICC, interclass correlation coefficient.

Table 4. ***Experimental results and calculated values from Appendix I.***

	Pdi (cm H_2O)	EAdi (a.u.)	CF_0 (Hz)	CF_∞ (Hz)	Q	Force ratios ϕ_I	ϕ_{II}	ϕ_m	Geometric factors γ_I (cm H_2O)	γ_{II} (cm H_2O)	γ_m
Volume Maneuver	31.2	60.9	100	74.2	0.175	6.12	5.20	5.66	122	144	133
Expulsive maneuver (Low pressure)	31.6	24.9	100	91.2	0.050	2.50	2.19	2.35	303	347	325
Expulsive maneuver (High pressure)	67.5	44.3	100	72.1	0.196	4.45	5.69	5.07	364	285	324

Pdi, transdiaphragmatic pressure; a.u., arbitrary units; EAdi, electrical activity of the diaphragm; $CFdi_0$, baseline diaphragm center frequency determined during resting breathing; $CFdi_\infty$, plateau value of the diaphragm center frequency at the end of the maneuver; Q, ratio of the time constants of CFdi recovery and decline, see equation (5); ϕ_I, see equation (9); ϕ_{II}, see equation (10); ϕ_m, mean of ϕ_I and ϕ_{II}; γ_I, see equation (14); γ_{II}, see equation (15); γ_m, mean of γ_I and γ_{II}.

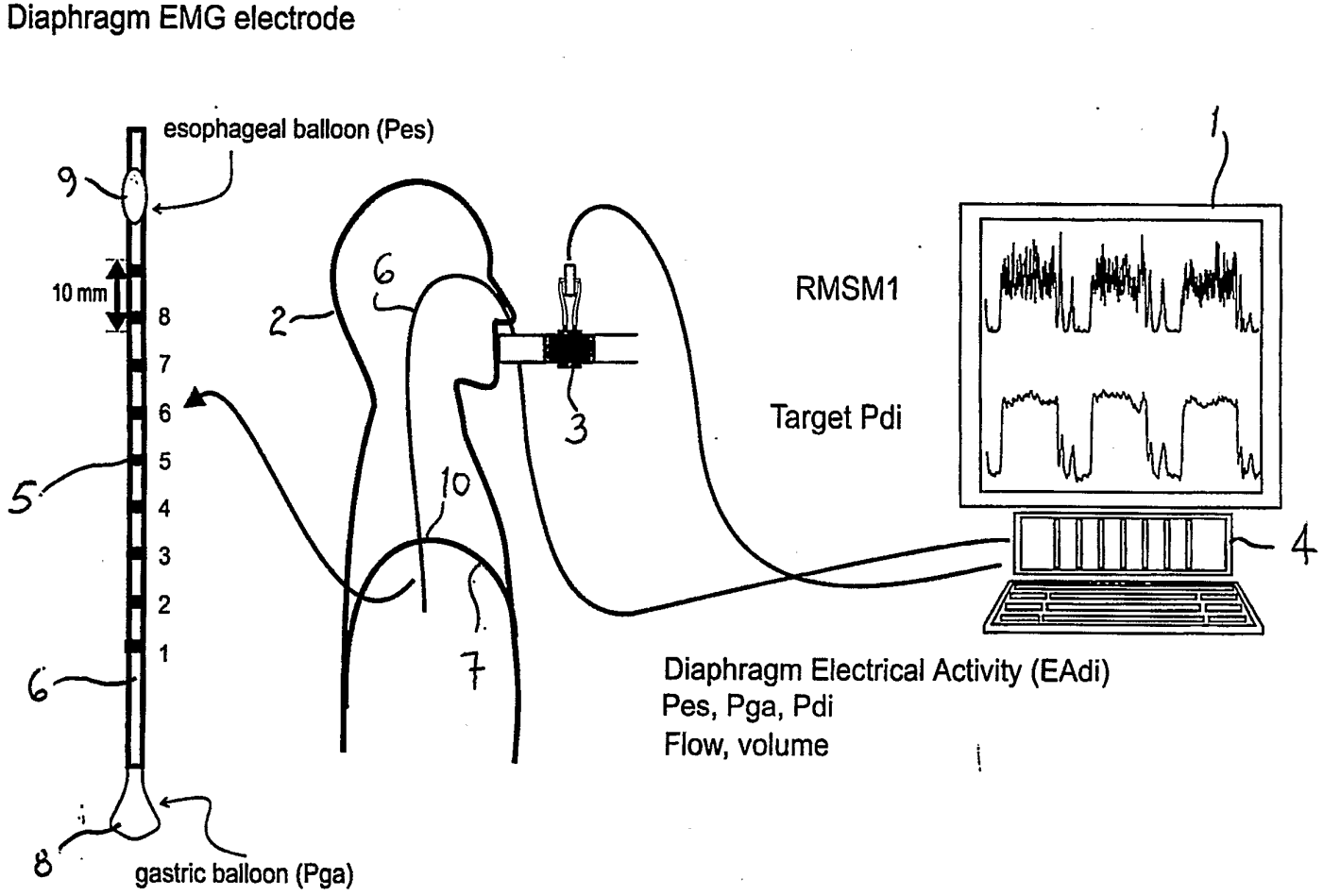

FIG: 1

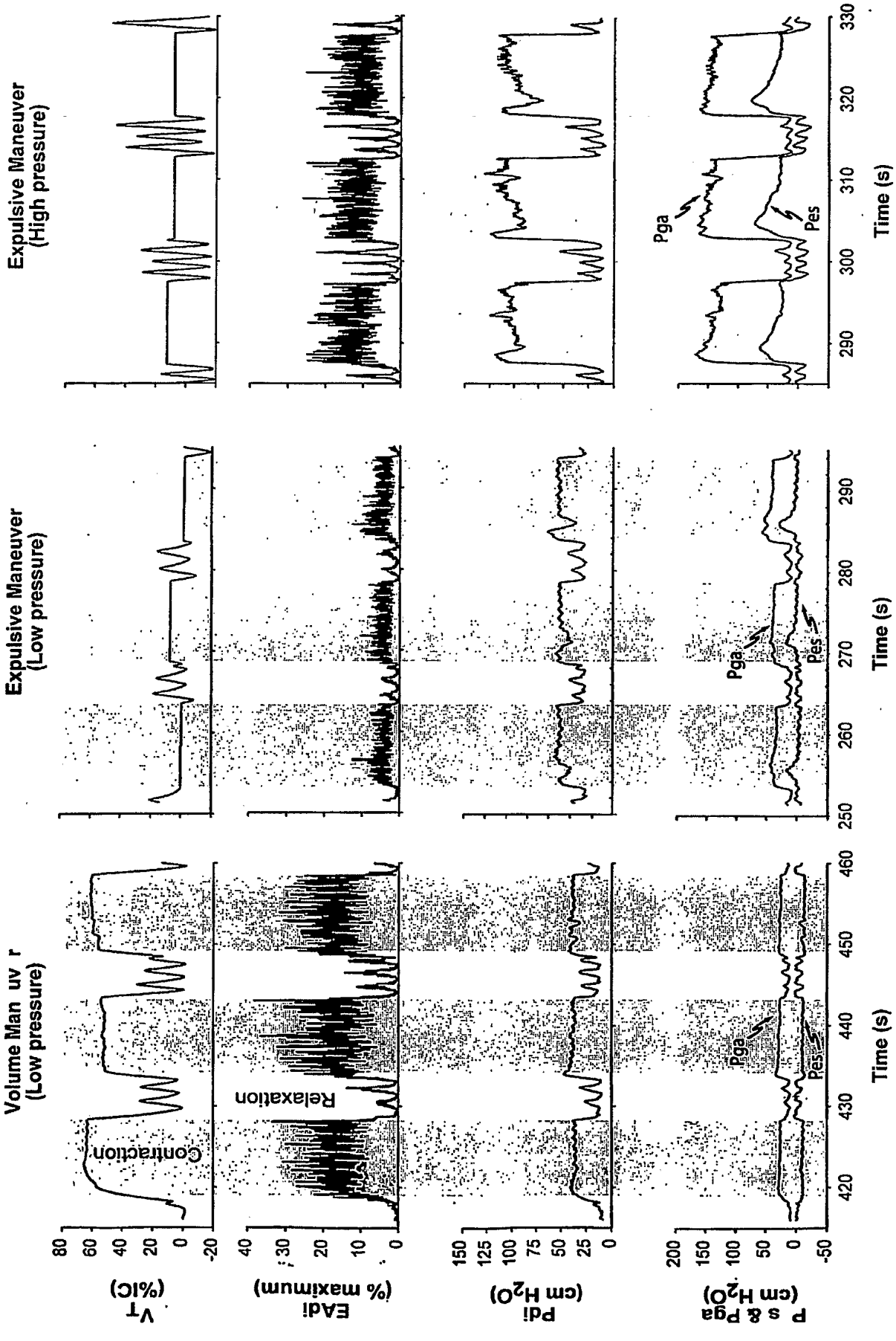

FIG: 2

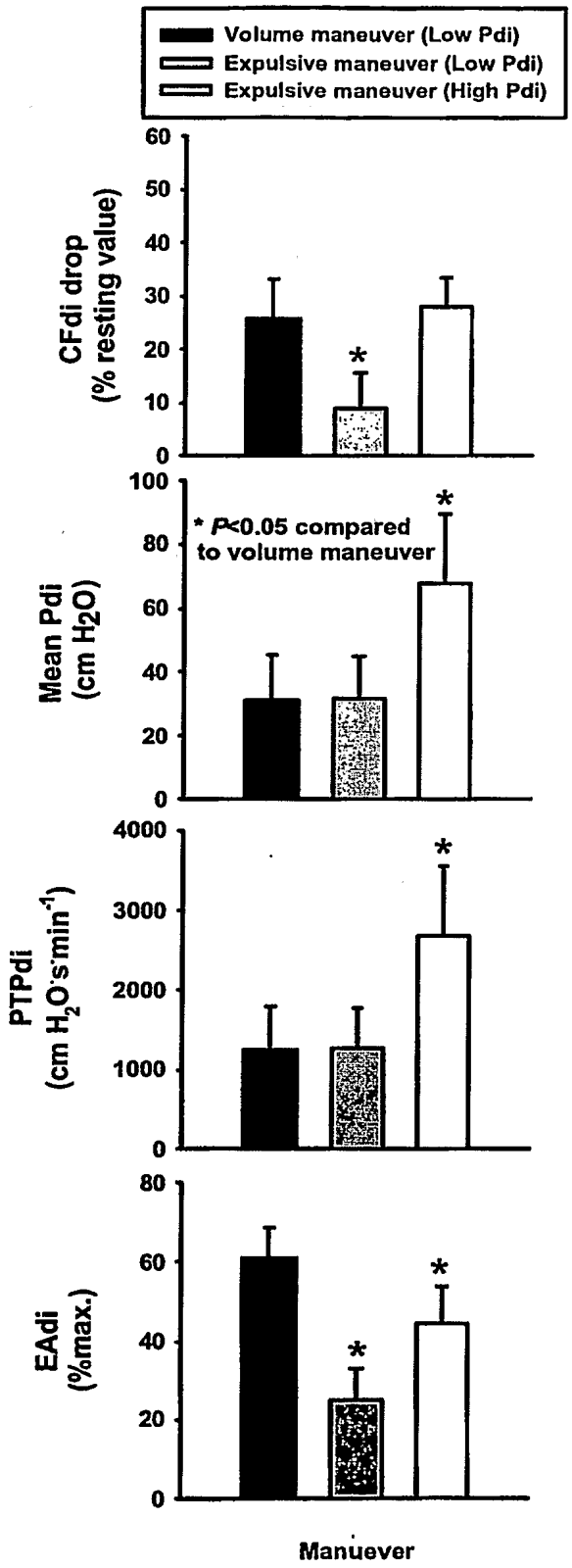

FIG: 3

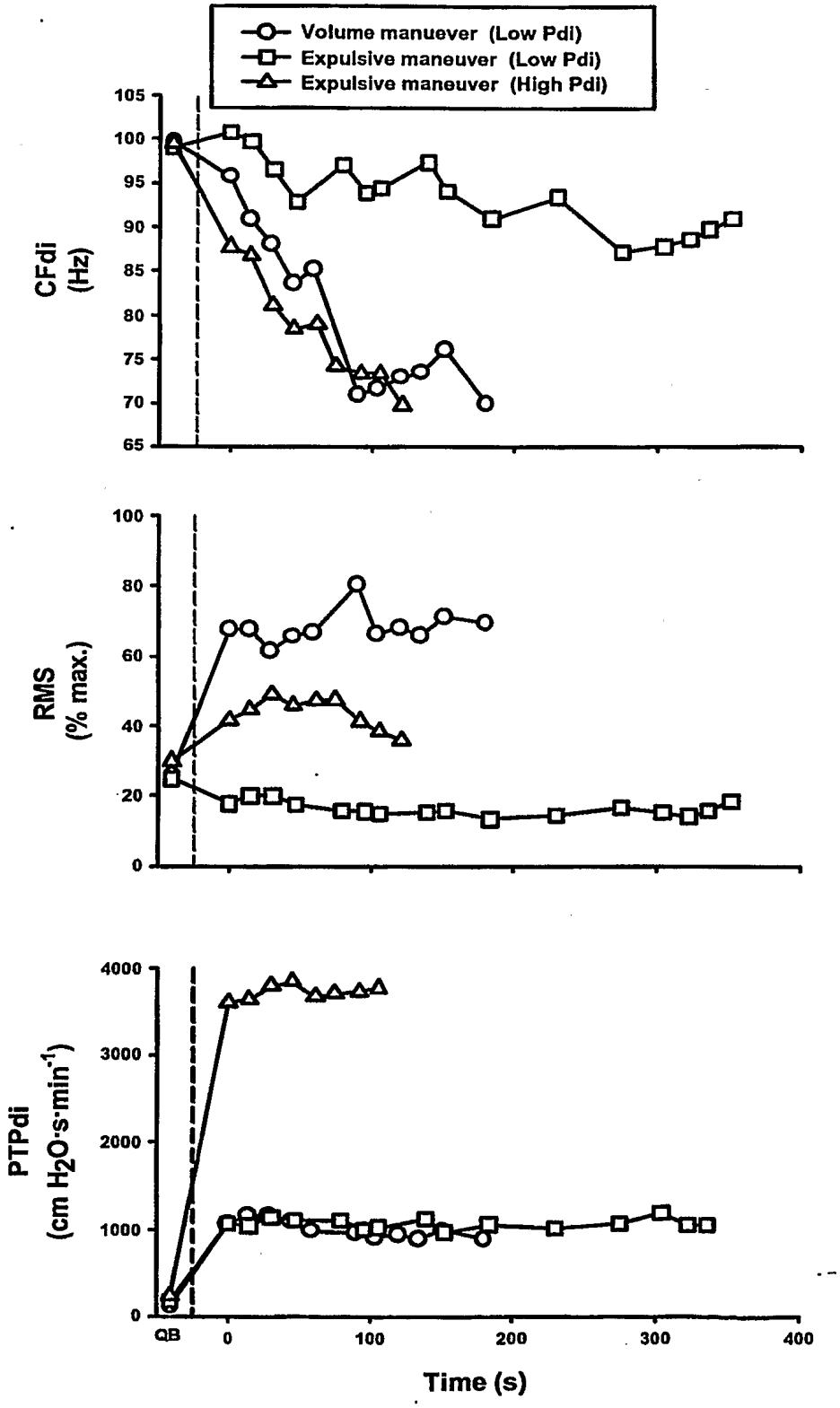

FIG: 4